Is the breast-conserving treatment with radiotherapy appropriate in mutation carriers? Long-term results and review of the literature

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CLINICAL TRIAL

Is the breast-conserving treatment with radiotherapy appropriate in *BRCA1/2* mutation carriers? Long-term results and review of the literature

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Abstract As tumours in *BRCA1/2* mutation carriers might be more sensitive to radiation, we investigated after long-term follow-up whether mutation status influenced the rate of ipsilateral and contralateral breast cancers after breast-conserving treatment (BCT). *BRCA1* and *BRCA2* genes were screened for germline mutations in 131 patients with a family history of breast and/or ovarian cancer who had undergone BCT and radiotherapy. Patients were matched to 261 controls with sporadic breast cancer according to age at diagnosis and year of treatment. Controls were followed up for at least as long as the interval between diagnosis and genetic screening in familial cases. Rates of ipsilateral and contralateral cancer between groups were compared by the log-rank test. The *BRCA1/2* mutations occurred in 20.6% of tested patients. Tumours in mutation carriers were more likely to be grade III ($P < 10^{-4}$) and oestrogen receptor negative ($P = 0.005$) than in non-carriers and controls. Overall median follow-up was 161 months. There was no significant difference in ipsilateral tumours between mutation carriers, non-carriers and controls ($P = 0.13$). On multivariate analysis, age was the most significant predictor for ipsilateral recurrence ($P < 10^{-3}$). The rate of contralateral cancer was significantly higher in familial cases: 40.7% (mutation carriers), 20% (non-carriers), and 11% (controls) ($P < 10^{-4}$). After 13.4 years of follow-up, the rate of ipsilateral tumours was no higher in mutation carriers than in non-carriers or controls. As tumours in *BRCA1/2* mutation carriers might be more sensitive to radiation, BCT is a possible treatment option.

Keywords BRCA1/2 mutations · Breast-conserving treatment · Radiotherapy · Recurrence

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Introduction

BRCA1 and *BRCA2* mutations are found in approximately 5% of all breast cancers and in up to 20–25% of tumours in patients with a family history of breast and/or ovarian cancer [1]. *BRCA1* mutation carriers develop tumours of a higher grade and proliferation index, with lower oestrogen receptor levels than patients with no such mutation, and tend to have worse outcomes [2–5]. *BRCA2* mutation carriers, on the contrary, present tumours with pathologic features similar to those of sporadic tumours [2–10].

Several studies suggest that *BRCA* gene mutation might influence response to radiation therapy because tumours in *BRCA1/BRCA2* carriers are more sensitive to ionising radiation [5–12]. The hypothesis that *BRCA* mutation is associated with increased radio sensitivity was supported by experimental and clinical data [12–19].

Breast-conserving surgery combined with radiation therapy is standard treatment for early stage breast cancer and provides equivalent survival to mastectomy [20–27]. We and other authors demonstrated that the recurrence rate in *BRCA1/BRCA2* carriers is not increased in this population of patients [28–32]. On the contrary, it is well known that after long latent period, the radiation therapy for breast cancer can induce malignant tumours after a latency of several years [33, 34]. The risk of second cancers in this population of patients is insufficiently documented [35, 36]. However, its safety in *BRCA* mutation carriers is a matter of debate, and several studies have compared ipsilateral tumour recurrence after breast-conserving treatment (BCT) in *BRCA1* and *BRCA2* mutation carriers and patients with sporadic cancers [9, 28–32, 37–41].

As tumours in *BRCA* mutation carriers might be more sensitive to radiation with increased risk of second primaries, we report after long-term follow-up whether mutation status influenced the rate of ipsilateral tumours after BCT. This analysis was planned in our previously reported study of homogeneous population of *BRCA1/2* mutation carriers and their controls, treated at the Institut Curie [28].

Patients and methods

Patients

We retrospectively analysed a cohort of women with small breast cancers treated with breast-conserving surgery and radiotherapy at the Institut Curie between 1981 and 2000. These patients had been invited to attend the family cancer clinic of our institute between 1990 and 2001 if they had a family history of breast or ovarian cancer. Patient selection criteria, genetic screening, and information retrieval methods (familial history, age at cancer diagnosis and death of relatives, and current age) have been described earlier [28, 42].

Genetic screening was offered to women who had either (i) two first-degree relatives affected by cancer, one with invasive breast cancer before 41 years of age or with ovarian cancer at any age, or (ii) at least three first- or second-degree relatives from the same lineage affected with invasive breast or ovarian cancer at any age. The index case was one of the affected family members. The probability of being a carrier of a breast cancer predisposing allele mutation was estimated by taking into account the segregation parameters of Claus modified by Easton and by using the MLINK programme [43–45]. Patients were informed about the aims and limitations of genetic screening. A blood sample was collected with their written consent.

A total of 131 patients who had undergone conservative surgery and radiotherapy in our institute (136 breast cancers) were screened. Each case was matched to two controls with no family history of breast cancer. One control had to be excluded because it did not meet our selection criteria, giving a total of 261 sporadic cases (271 breast tumours). Controls were randomly selected from our prospective breast cancer registry of 9179 patients who underwent conservative treatment between 1981 and 2000, as reported earlier [28, 46]. Matching factors included age at diagnosis, year of treatment, and period of follow-up between cases and controls. *BRCA* status was known in only one patient at diagnosis and treatment. Clinical, pathological, and outcome data were recorded.

All the cases were treated during the same year as their matched controls using the same protocol. Patients underwent wide surgical excision of the primary tumour and, in most cases, axillary lymph node dissection. This was followed by breast irradiation and by regional node irradiation in the cases of node involvement with doses and techniques already described [28, 47–49]. A boost was delivered to the tumour bed whenever indicated. Controls were followed up for at least as long as the time between diagnosis and genetic screening in familial cases.

Statistical analysis

Patient and tumour characteristics were compared by a chi-square or Fisher's exact test for qualitative variables and by ANOVA (comparisons of means) or the Kruskal–Wallis test (comparisons of medians) for quantitative variables.

Survival was determined from the date of diagnosis to the date of death or last follow-up. Ipsilateral recurrence-free interval was defined as the period from the date of diagnosis of breast cancer to the date of the first local recurrence. Time to recurrence was censored at the time of any event prior to local recurrence (death, lymph node recurrence, distant recurrence, contralateral tumour, or second cancer) or at the time of last follow-up. The contralateral tumour-free interval was defined as the period from the date of diagnosis to the date of contralateral breast cancer. In the 5 patients with bilateral cancer at diagnosis, one tumour was considered to be a contralateral tumour occurring at diagnosis (time to event equal to zero).

The Kaplan–Meier method was used to assess the overall survival, ipsilateral recurrence-free survival and contralateral tumour-free survival rates. Event-free survival

times of *BRCA* mutation carriers, non-carriers with a history of familial breast cancer and controls with sporadic disease were compared using the log-rank test [50, 51]. The influence of *BRCA* mutation, adjusted for other prognostic factors, was assessed in a multivariate analysis by the Cox proportional hazards model, in a forward stepwise regression procedure [52]. Age, histological nodal status, oestrogen and progesterone receptor status, and Scarff–Bloom–Richardson grading were entered into the model. Categorical variables were transformed into dummy variables to avoid any assumption concerning the estimation of the relative risks (RRs) between subgroups. Missing values were coded as separate variables when necessary.

We used Splus 2000 software (MathSoft Inc., Seattle, WA).

Results

Twenty-seven patients (20.6%) with a family history of breast cancer had a *BRCA* mutation (19 *BRCA1*, 8 *BRCA2*) (21.3% tumours). As expected, the median probability of being a *BRCA* carrier was significantly higher in carriers than in non-carriers with a family history of breast cancer (90 [73–98] versus 55 [6–98], $P = 0.002$).

Patients' characteristics were well balanced in the three groups. Median age was 43 years [range, 26–60] in *BRCA1/2* mutation carriers, 43.5 years [24–78] in non-carriers and 43 years [23–79] in controls ($P = 0.92$). The percentage of patients who were pre-menopausal was 85, 70 and 76%, respectively ($P = 0.24$). As reported earlier, the familial and sporadic cohorts were well matched with regard to age at diagnosis [26]. Overall median follow-up was 161 months [range 31–297] and was broken down as follows: 167 months [35–230] for *BRCA* mutation carriers, 161 months [35–270] for non-carriers and 156 months [32–297] for controls. Two *BRCA1* carriers and 3 non-carriers had synchronous bilateral breast cancers.

Table 1 gives tumour characteristics according to *BRCA1/BRCA2* mutation status. The 27 mutation carriers had 29 tumours. These tumours were more likely to be grade III ($P < 10^{-4}$) and receptor negative ($P = 0.02$) than tumours in either non-carriers or controls, and to be of the medullary subtype. All medullary tumours in patients with familial cancer occurred in patients with *BRCA1* mutations. Treatment did not differ significantly amongst groups (Table 2). The only observed difference in hormonal treatment, probably related to hormonal status in carriers (mostly hormonal negative tumours) was not analysed because of the small size of patients in the three groups.

There was no significant difference in ipsilateral tumour recurrence amongst groups ($P = 0.13$) nor between mutation carriers and their matched controls ($P = 0.43$) (Fig. 1a, b). Crude recurrence rates and hazard ratios are given in Table 3 as well as the site of recurrence. Most patients experienced recurrence in the same quadrant as the initial tumour. There was no difference in site according to group. Three of the 6 patients with medullary carcinoma had an ipsilateral recurrence: one in the control group at 79 months and two in the mutation carrier group at 91 and 245 months. In a uni- and multivariate analysis, age was the only significant predictor for local recurrence. The RR of recurrence was 1.05 [1.02–1.07], ($P < 10^{-3}$) for each decreasing year of age. *BRCA* mutation status, lymph node status, hormonal receptor status and tumour grade were not significant predictors of local recurrence.

The rate of contralateral breast cancer was significantly higher in mutation carriers than in non-carriers and controls ($P < 0.0001$) and higher in mutation carriers than in their matched controls ($P = 0.0011$) (Fig. 2a, b). There were 40.7% in the group of *BRCA1/2* mutation carriers versus 20.2% in familial cases versus 11.1% in the group of sporadic controls ($P < 10^{-4}$). In a uni- and multivariate analysis, *BRCA* mutation status was the only significant predictor for the risk of developing a contralateral cancer ($P < 10^{-4}$). Age, lymph node status, hormonal receptor status and tumour grade were not significant predictors.

The role of tamoxifen in the risk of contralateral breast cancer has not been studied because of the increased number of receptor-negative tumours.

There was no significant difference in the overall survival between the three groups (Fig. 3).

Discussion

This matched retrospective case-control single institutional study with an overall median follow-up of 13.4 years has shown that the rate of ipsilateral tumours was no higher in *BRCA1* and *BRCA2* mutation carriers than in non-carriers with a family history of breast cancer and in matched controls, despite the fact that tumours with *BRCA1* mutations tend to be more aggressive. In order to avoid bias, controls were followed up for at least as long as the time interval between diagnosis and genetic screening in familial breast cancer cases. Our study confirmed the earlier reported increased incidence of contralateral breast cancers. At the same time, there was no difference in the overall survival in the different groups of patients. The main weakness of our study is the limited number of patients and its retrospective nature.

The main case–control studies on ipsilateral tumour recurrence are summarized in Table 4. Our long-term results support the findings of a multi-institutional study in which no significant difference in ipsilateral recurrence was noted between *BRCA1/2* mutation carriers ($n = 170$)

Table 1 Tumour characteristics

	BRCA1/2-mutated tumours $n = 29$	Non-mutated tumours $n = 107$	Sporadic controls $n = 271$	*P*
T stage UICC—*n* (%)				
No palpable tumour	3 (10.3)	17 (15.9)	49 (18.1)	0.85
T1-2	26 (89.7)	85 (79.4)	212 (78.2)	
T3	0	0	1 (0.4)	
Tx	0	5 (4.7)	9 (3.3)	
Clinical tumour size (mm)				
Median [Range]	20 [0–35]	15 [0–35]	20 [0–70]	0.49
N stage—*n* (%)				
N0	26 (89.7)	89 (84)	243 (70.5)	0.22
N1	3 (10.3)	17 (16)	26 (29.5)	
Nx				
Pathological nodal status—*n* (%)				
Negative	21 (72.4)	49 (45.8)	133 (49.1)	0.13
Positive	3 (10.3)	20 (18.7)	41 (15.1)	
No lymph node dissection	5 (17.2)	38 (35.5)	97 (35.8)	
Pathology—*n* (%)				
Ductal invasive	17 (65.4)	77 (84.6)	216 (82.1)	$<10^{-3}$[a]
Lobular invasive	3 (11.5)	10 (11.0)	16 (6.1)	
Medullary	3 (11.5)	1 (1.1)	2 (0.8)	
Other	2 (7.7)	1 (1.1)	12 (4.5)	
DCIS	1 (3.9)	2 (2.2)	17 (6.5)	
ND	3	16	8	
Histological grade—*n* (%)				
I, II	9 (31.1)	67 (76.1)	166 (81.0)	$<10^{-4}$
III	14 (68.9)	21 (23.9)	39 (19.0)	
'non gradable' + ND	6	19	66	
Oestrogen receptors—*n* (%)				
Negative	11 (47.8)	19 (27.5)	33 (20.9)	0.018
Positive	12 (52.2)	50 (72.5)	125 (79.1)	
ND	6	38	113	
Progesterone receptors—*n* (%)				
Negative	11 (47.8)	15 (21.7)	34 (21.7)	0.02
Positive	12 (52.2)	54 (78.3)	123 (78.3)	
ND	6	38	114	

[a] The medullary subtype was more common in *BRCA1* carriers than in other groups (11.5 vs. 1.1 vs. 0.8%, $P = 0.005$)

ND not determined

Table 2 Treatment

	BRCA1/2-mutated tumours $n = 29$	Non-mutated tumours $n = 107$	Sporadic controls $n = 271$	*P*
Node irradiation				
No	15 (51.7)	40 (37.4)	108 (39.9)	0.40
Yes	14 (48.3)	67 (62.6)	163 (60.1)	
Whole breast dose [Gy]				
Median [range]	52 [45–62]	52 [43–62]	52 [45–66]	0.87
Tumour dose [Gy]				
Median [range]	65 [50–75]	64 [50–78]	65 [45–82]	0.75
Boost to tumour bed (%)	72	61	66	0.6
Chemotherapy (%)	38	28	25	0.29
Hormonal therapy (%)	7	13	6	0.045

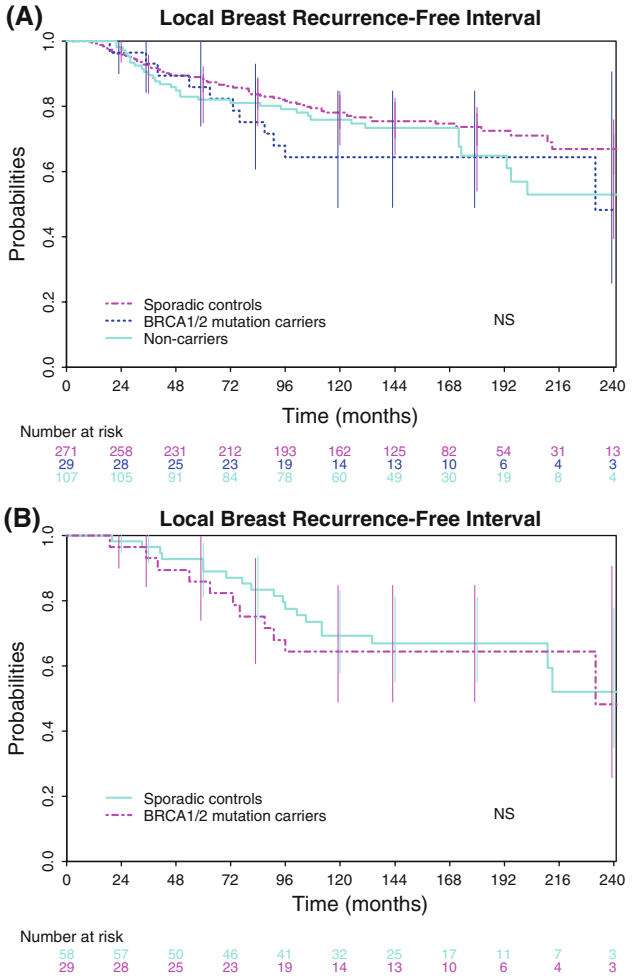

Fig. 1 Ipsilateral recurrence rate: **a** *BRCA1/2* mutation carriers versus non-carriers versus sporadic controls, **b** *BRCA1/2* mutation carriers versus their matched sporadic controls

Table 3 Description of ipsilateral tumours and their site

	BRCA1/2-mutated tumours $n = 29$	Non-mutated tumours $n = 107$	Sporadic controls $n = 271$	p
Ipsilateral				
Number	13	33	66	
Hazard ratio	1.8 [1–3.3]	1.3 [0.8–2.0]	1	
Site				
Same quadrant	11	21	48	0.33
Other quadrant	2	12	18	

and sporadic cases matched by age and date of diagnosis ($n = 469$) after a median follow-up of 8.3 years, reported by Pierce et al. [30]. Matched cohort study described increased recurrence, after adjustment for age, in the hereditary group at 5 years but no significant increase in the 26 *BRCA1/2* mutation carriers compared to sporadic cases [38]. The more recent publication of the same team

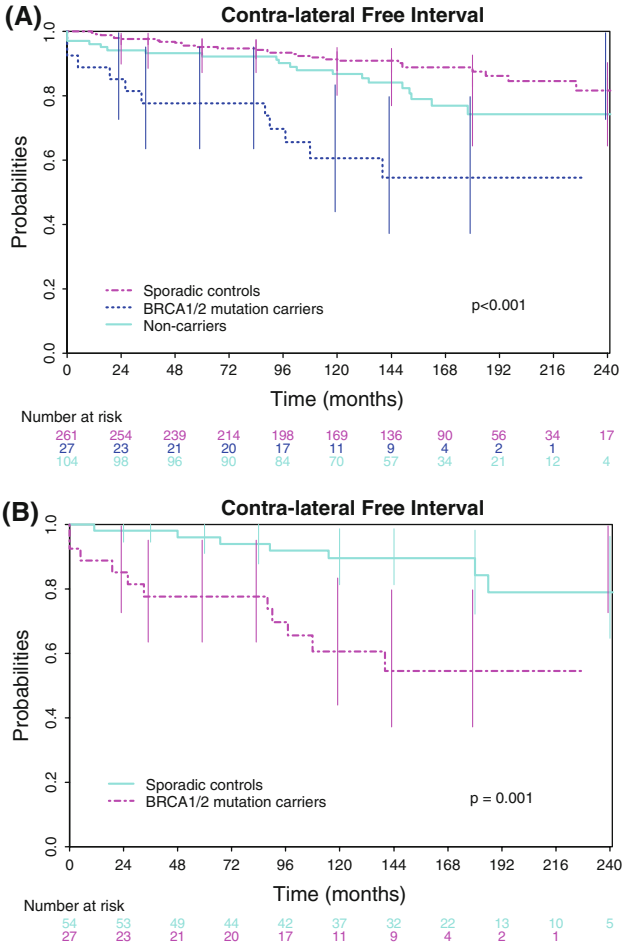

Fig. 2 Contralateral tumour free interval: **a** *BRCA1/2* mutations carriers versus non-carriers versus sporadic controls, **b** *BRCA1/2* mutation carriers versus their matched sporadic controls

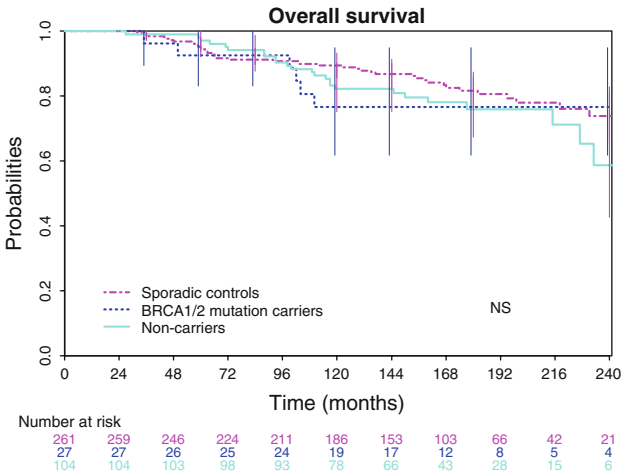

Fig. 3 Overall survival in *BRCA1/2* mutation carriers versus non-carriers versus sporadic controls

reported by Brekelmans et al. [31] showed no difference in term of ipsilateral breast recurrence, $P = 0.6$ between carriers and controls. Recently published new study of very

Table 4 Main retrospective studies of ipsilateral recurrence in *BRCA* carriers treated by BCT and radiotherapy

	Study period and type	BRCA1/2 carriers (*N*)	Controls (*N*)	Median follow up (years)	Ipsilateral recurrence (%)		*P*
					Carriers	Controls	
Haffty et al. [37]	1975–1998	22	105	13	49	21	0.007
Robson et al. [9]	1980–1995	56	440	9.7	12	8	0.68
Seynaeve et al. [38]	1980–1995 Matched	26	174	6.0	21.8	12.1	0.05
Brekelmans et al. [31]	1980–2004 Matched	109 (76/33)	410	4.3	12/17	12	0.6
Pierce et al. [30]	1980–1997 Matched	170	469	8.3	12.5	8.6	0.55
Kirova et al. [28]	1981–2000 Matched	29 (107)[a]	271	8.8	24	19	0.47
This study	1981–2000 Matched	29	58	13.4	36	33	0.42

[a] Familial cases

young patients by Garcia-Etienne et al. [41] suggested after median follow-up of 4 years increased rates of ipsilateral breast cancer incidence in mutation carriers (9.3 vs. 2.5%) without complete information concerning the radiotherapy modalities (total dose, boost to the tumour bed) is given.

The results of the two non-matched cohort studies in Table 4 are contradictory, no significant difference being found in the Robson et al. study unlike in the Haffty et al. study of a subgroup of 127 patients under 42 years of age [9, 37]. In the latter study, the significantly higher ipsilateral recurrence rate in *BRCA1/2* mutation carriers suggests that there might be an increase in the rate of second primary cancers after 10 years. In this study and also in other series, age was a significant predictor of recurrence, supporting the observation that young age rather than *BRCA* status is a strong predictive factor for local relapse in hereditary breast cancer patients [28, 32].

We observed a significantly higher incidence of contralateral breast cancer in *BRCA1/2* carriers than in non-carriers and controls. All studies of *BRCA1* and/or *BRCA2* mutation carriers so far have reported an increased incidence of contralateral breast cancer [9, 15, 28–30, 37, 38, 40]. Pierce et al. [30] have reported 10-year actuarial estimates of 26 and 3% for carriers and sporadic controls, respectively ($P < 0.0001$). Robson et al. [9] reported a 27% risk in carriers versus an 8% risk in non-carriers ($P = 0.002$) after 10 years of follow-up. Haffty et al. [37] recorded a 42% rate in carriers versus a 9% rate in non-carriers ($P = 0.001$) at 12 years. The high risk of contralateral breast cancer in *BRCA1*/*BRCA2* mutation carriers must be taken into account when choosing treatment. If the choice is breast conservation, strategies such as prophylactic oophorectomy and tamoxifen administration with close radiological surveillance should be discussed with the patient [53–55]. Mutation carriers do have a choice as no difference has been noted in overall survival compared to controls. The issue is complex and has been masterly addressed in a recent article [56].

With the new advances in the knowledge of hormonal receptor negative and HER2 negative tumours, new treatment possibilities could be offered this population of patients. The published data suggest that PARP inhibitors could be used not only as chemo/radiotherapy sensitizers, but also as single agents to selectively kill cancers defective in DNA repair, specifically cancers with mutations in the breast cancer associated (BRCA) 1 and 2 genes. This theory of selectively exploiting cells defective in one DNA repair pathway by inhibiting another is a major breakthrough in the treatment of cancer. BRCA1/2 mutations are responsible for the majority of genetic breast/ovarian cancers, known as the hereditary breast ovarian cancer syndrome [57].

In summary, our long-term study has confirmed that the rate of ipsilateral tumour recurrence in *BRCA1* and *BRCA2* mutation carriers is no higher than in non-carriers or patients without a family history of breast cancer despite the more aggressive features of these tumours. It has also confirmed the higher risk of contralateral breast cancer in mutation carriers. This calls for risk reduction strategies. Since tumours in *BRCA* carriers appear to be more sensitive to radiation, BCT may be considered in *BRCA* mutation carriers after discussion with the patient.

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